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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,857	12/11/2003	Michael Patane	CASM122094	8103

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,857	PATANE, MICHAEL	
	Examiner	Art Unit	
	Allison M Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-20* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-16* is/are rejected.

7)☒ Claim(s) 6 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Response to Amendment

Applicant's amendments to claims 1, 11-12 and 15-16 have been entered. Claims 3-5 have been cancelled. Applicant's arguments filed 1/20/05 have been fully considered but they are not persuasive.

Claim Objections

Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicant argues that 5mM, as taught by Holle et al is not "about 10 mM," as required by the claim since 10 mM is more than 2 fold greater than 5 mM. However, because the claimed concentration ranges from 10 to 50 mM, a span of 40 mM, a margin of +/- 5 mM is considered reasonable. Therefore the interpretation of "about 10 to 50 mM" to include 5 mM to 55 mM is believed to be conservative and acceptable.

Therefore, claims 1 & 7-10 are still rejected under 35 U.S.C. 102(b) as being anticipated by Holle et al (US Patent 3,516,907).

Applicant's claim 1 is now directed to a process for purifying a phosphodiesterase 1 (PDE-1) from a cell including heating an extract of a cell formed from a solution including at least one divalent

cation, to increase the specific activity of PDE-1 in the extract, wherein the concentration of the divalent cation is about 10 to 50 mM. Claim 7 requires the extract to be heated to a temperature that permits depletion of phosphomonoesterase activity from the extract. Claim 8 requires the extract to be heated to between about 45°C and 75°C. Claim 10 requires the extract to be heated to about 60°C.

Holle et al teach a process for purifying a phosphodiesterase 1 (PDE-1) from crude extract of vegetable cells, including barley cells (See col. 2, ln 49-55), comprising heating an extract of a cell containing 5'-phosphodiesterase (which applicant refers to as PDE-1, See IUMBM Enzyme Nomenclature, EC 3.1.4.1) in a solution containing a heavy metal salt, such as $ZnCl_2$, $CuCl_2$, and $MnCl_2$, (Zn^{2+}, Cu^{2+}, and Mn^{2+} being divalent cations) at a temperature between 55 and 65°C (See col. 2, ln 1-15, and col. 10, ln 36-48) (Claims 1 & 7-10). Holle et al teach the concentration of the heavy metal salts to be between 2 mM and 5 mM (See col. 3, ln 46-48); 5 mM is being defined by the examiner to be about 10 mM (Claim 1). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant argues that a concentration of divalent cations of 5mM, as taught by Holle et al is not "about 10 mM," as required by claims 1 and 11, since 10 mM is more than 2 fold greater than 5 mM. Also, applicant traverses the statement that the concentration of the metal cation is result effective, without evidence to the fact. Still further, applicant argues that Holle et al does not teach the specific divalent cations in the claimed invention.

The examiner maintains that 5 mM is "about 10 to 50 mM." Because the claimed concentration ranges from 10 to 50 mM in claims 1 and 11, a span of 40 mM, a margin of +/- 5 mM is considered reasonable. Therefore the interpretation of "about 10 to 50 mM" to include 5 mM to 55 mM is believed to be conservative and acceptable.

For a rejection under 35 U.S.C. § 103 it is not required that a single reference teach all the limitations of the invention, but rather the combination of references renders the whole invention *prima facie* obvious. Therefore, though Holle et al does not provide evidence that the divalent cations can be selected from magnesium, calcium, or a combination of magnesium and calcium, Harvey et al teach the use of divalent metal ions, including magnesium and calcium, to increase the specific activity of the PDE-1 enzyme (See Harvey et al, Pg. 3692, col. 1, & Table II). Harvey et al teach PDE-1 is normally tightly bound to EDTA in the crude extract solution, addition of divalent cations competitively bind to the EDTA, freeing the PDE-1 (See Pg. 3692, col. 1). Additionally, Harvey et al provide evidence that the concentration of the magnesium ions does affect the specific activity of the enzyme; the specific activity of the enzyme increases with increased concentration of $MgCl_2$, to reach a maximum activity at approximately 40 mM $MgCl_2$ (See Harvey et al, Pg. 3692, Fig. 4). Therefore the concentration of the divalent cation is a result effective variable, increasing the concentration, up to approximately 40 mM increases the specific activity of the PDE-1; therefore one of ordinary skill in the art would have been motivated to increase the concentration of the divalent cations in the method of Holle et al from 5 mM to 10 mM and up to 50 mM. This is in agreement with applicant's findings that extraction solutions

containing divalent cation concentrations of 50 mM, the specific activity of the PDE-1 was found to be 40% higher than when extraction solution contained only 5 mM divalent cation (See Spec Pg. 11, ln 17-20).

Additionally, applicant argues that Holle et al do not teach or suggest that the divalent cation has a role in protecting PDE-1 from heat denaturation, nor do they teach or suggest that the heating step is to be used for denaturation of enzymes. Though Holle et al does not teach the use of the divalent cations for the purpose of protecting the PDE-1 enzyme from denaturation during heating, nor do they suggest that the heating step is used for denaturation of the enzymes, the protective effect of the divalent cations on the enzyme and denaturing effect of the heating to temperatures of about 60°C are inherent. Therefore, because the method of Holle et al does comprise the steps of adding divalent cations to the crude enzyme extract, and heating at temperatures of about 55-65°C (See col. 2, ln 1-15), the same inherent results are achieved, whether they are explicitly taught or suggested, or not. Therefore Holle et al teach the same process of purifying PDE-1 as in the current application, and thus the PDE-1 formed by Holle et al is one and the same as the PDE-1 formed in the current application. See *Atlas Powder Co v. Ireco, Inc*, 190 F.3d 1342, 1348-49 (Fed. Cir. 1999).

Therefore claims 1, 2 and 7-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Holle et al (US Patent 3,516,907), in view of Harvey et al (*Biochemistry*, 1967) and De-Eknamkul et al (US Patent 5,879,916), and in light of Hsin et al (*Blood*, 1998).

Applicant's claim 1 is now directed to a process for purifying a phosphodiesterase 1 (PDE-1) from a cell including heating an extract of a cell formed from a solution including at least one divalent cation, to increase the specific activity of PDE-1 in the extract, wherein the concentration of the divalent cation is about 10 to 50 mM. Claim 2 requires the divalent cation to be magnesium or calcium. Claim 7 requires the extract to be heated to a temperature that permits depletion of phosphomonoesterase activity

from the extract. Claim 8 requires the extract to be heated to between about 45°C and 75°C. Claim 10 requires the extract to be heated to about 60°C. Claim 11 is directed to a process for purifying PDE-1 from a barley cell, including releasing PDE-1 from the cell into a solution including about 10 to 50 mM of calcium and about 10 to 50 mM magnesium to form an extract; and heating the extract to between about 45 to 70°C increase the specific activity of PDE-1 in the extract. Claim 12 requires the extract to be maintained in conditions for promoting solubilization of the phosphodiesterase in the extract prior to heating the extract. Claim 13 requires the extract to be maintained at less then 10°C. Claim 14 requires the extract to be maintained at temperatures between 0 to about 4°C. Claim 15 requires the further step of chromatography to purify PDE-1 from the heated extract. Claim 16 requires the chromatography to be anion exchange chromatography.

Holle et al teach a process for purifying a phosphodiesterase 1 (PDE-1) from crude extract of vegetable cells, including barley cells (See col. 2, ln 49-55), comprising heating a cell extract containing 5'-phosphodiesterase in a solution containing a heavy metal salt, such as $ZnCl_2$, $CuCl_2$, and $MnCl_2$, (Zn^{2+}, Cu^{2+}, and Mn^{2+} being divalent cations) at a temperature between 55 and 65°C (See col. 2, ln 1-15, and col. 10, ln 36-48) (Claims 1 & 7-10). Holle et al teach the concentration of the heavy metal salts to be between 2 mM and 5 mM (See col. 3, ln 46-48). Though Holle et al describe using between 2 mM and 5 mM of heavy metal salts, it would have been obvious to one of ordinary skill in the art to experiment with slightly higher concentrations of metal salts up to and including a concentration of 10 mM. One would be motivated to manipulating the concentration within a reasonable range, such as +/- 5 mM, because Harvey et al clearly indicates that the various proportions and amounts of the divalent cations used in the claimed composition are result effective variables, wherein higher concentrations of divalent cations increase the specific activity of the PDE-1 enzyme, with a maximum activity obtained at about 40 mM (See Harvey et al Pg. 3692, col. 1 & Fig. 4). Therefore the concentrations of the divalent cations would

be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by Holle et al in view of Harvey et al.

Holle et al further purify PDE-1 from the heated barley extract containing divalent cations by running the extract solution on an anion exchange chromatography column, Sephadex DEAE, Type A50 (See col. 5, ln 70- col. 6, ln 9) (Claims 11, 15-16). Holle et al does not explicitly say the Sephadex DEAE, Type A50 is an anion exchange column and Sephadex is no longer an independent company publishing a catalog, however, Hsin et al (*Blood,* 1998) reference use of the Sephadex DEAE, Type A 50 column and do specifically state it is an anion exchange chromatography column (See Hsin et al, Pg 3269, col. 1).

Though Holle et al teach using divalent cations, he does not specifically teach magnesium or calcium. However Harvey et al teach divalent cations, such as magnesium and calcium, increase the specific activity of the PDE-1 enzyme (See Harvey et al, Pg. 3692, col. 1, & Table II). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute magnesium or calcium chloride, for the zinc, copper, and manganese chlorides used by Holle et al. The person of ordinary skill in the art would have been motivated to substitute magnesium or calcium chloride for zinc, copper, and manganese chloride in order to cut back on the toxicity risks of zinc and manganese, or if they had magnesium chloride or calcium chloride more readily available in their laboratory (Claims 2 & 11). One would expect success because they are all divalent cations, and Holle et al has taught success using zinc, copper, and manganese, and Harvey et al teach magnesium and calcium also increase the specific activity of PDE-1 (See Holle et al, col. 2, ln 1-15, and col. 10, ln 36-48; & See Harvey et al, Pg. 3692, col. 1, & Table II).

It would have further been obvious to one of ordinary skill in the art at the time the invention was made to add both calcium and magnesium to the extract solution prior to heating, in the method of Holle et al (Claim 11). A person of ordinary skill in the art would have been motivated to add both divalent

cations in order to further increase the specific activity. One would have expected success because Harvey et al teach they both increase specific activity of PDE-1 (See Harvey et al, Pg. 3692, col. 1 & Table II), and there is no evidence they counteract one another.

Holle et al do not describe maintaining the extract solution in conditions that would promote solubilization of the phosphodiesterase in the extract prior to heating, their focus was more on heating. However, it is advantageous to maintain the extract solution at low temperatures prior to heating because low temperatures inhibit the action of proteolytic enzymes present in the crude extract (See De-Eknamkul et al). Active proteolytic enzymes could have a negative effect on the desired enzymes. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to maintain the extract solution at low temperatures prior to heating the extract (Claim 12). De-Eknamkul et al teach maintaining enzymes at 0-10^{0}C, optimally at 4°C to prevent unwanted enzymatic activity during enzyme extraction (See De-Eknamkul et al, col. 3, ln 12-29) (Claims 13 & 14). The person of ordinary skill in the art would have been motivated to maintain the enzymes at temperatures between 0-10°C, optimally at 4°C to allow more time for solubilization and extraction, without the threat of other enzymes in the crude extract acting destructively. One would expect success because De-Eknamkul et al teach temperatures between 0-10^{0}C, optimally 4^{0}C, do prevent the majority of enzyme activity (See col. 3, ln 25-27).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER